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Application No.: 10/787,385
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Steven C. Quay, *et al.* U.S. Patent Application Serial No.: 10/787,385 Filed: 02/26/2004 Title: CYANOCOBALAMIN LOW VISCOSITY AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY Attorney Docket No.: 03-02US	Assignee: Nastech Pharmaceutical Company Inc. by assignment reel/frame 014839 / 0972 Art Unit: 1623 Confirmation No.: 4791 Examiner: Paul V. Ward

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF ANTHONY SILENO, M.S. UNDER 37 C.F.R. § 1.132

Dear Sir:

I, Anthony Sileno, M.S., declare as follows:

1. I am presently employed by Nastech Pharmaceutical Company Inc. (hereafter "Nastech") as Senior Director of Clinical Affairs and Toxicology. I presently oversee pre-clinical and clinical development programs at Nastech, including a Phase I clinical unit directed to screening drug formulations for pharmacokinetic and pharmacodynamic evaluation. I have designed and conducted various pre-clinical and clinical Phase I-III studies successfully supporting IND and NDA applications with the United States Food and Drug Administration. In more specific aspects of my work, I have designed and implemented pre-clinical studies at Nastech to assess pharmacokinetics and pharmacodynamics of formulations, methods and devices for intranasal drug delivery--including the formulations, methods and devices for intranasal drug delivery of cyanocobalamin described in the above-referenced United States Patent Application Serial No. 10/787,385 entitled CYANOCOBALAMIN LOW VISCOSITY AQUEOUS FORMULATIONS FOR INTRANASAL DELIVERY, filed on February 26, 2004 (hereafter "the '385 application"). My CV summarizing my academic and industry experience is attached hereto as Appendix A).

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2. I am a named inventor in the '385 application, and I have carefully reviewed and analyzed the complete file history of the '385 application. In particular, I have reviewed and fully understand the '385 specification and all claims presented in this application, including the currently pending claims 1-31 (as set forth in the Current Listing of Claims presented in the Response to Office Action filed contemporaneously herewith). I have also reviewed all substantive Office Actions in the '385 application, including the most recent Office Action mailed July 31, 2006 (Paper No./Mail Date 20060722), to which my remarks herein, below are directed.

3. In the July 31, 2006 Office Action, Examiner indicates that all prior grounds for rejection of claims in this application have been overcome, with the exception of a single rejection in the current Office Action of claims 1, 23, 24, 30 and 31 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. This Declaration therefore focuses on the sole remaining issue in this application, relating to "enablement" of claims 1, 23, 24, 30 and 31.

4. Claims 1, 23, 24, 30 and 31 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the "enablement" requirement with respect to the claimed solution having a bioavailability, when administered intranasally, "of at least 7% relative to an intramuscular injection." (Office Action at p. 2.) Examiner presents the following remarks in support of this rejection (at pp. 2-4, underscores added).

> The claims are directed to a solution that, when administered intranasally, have (sic) a bioavailability of at least 7% relative to an intramuscular injection. An adequate representation regarding the bioavailability claimed would be one that provides all of the data necessary to calculate the bioavailability claimed relative to that of an intramuscular injection.
>
> Additionally, there are several methods of assessing bioavailability in humans and other animals. The selection of methods depends on the nature of the drug product and makes use of such parameters as time of peak plasma concentration, peak plasma concentration and the area under the plasma-time cure(sic) (AUC). However, Applicant does not provide any AUC data for bioavailability of cyanocobalamin delivered via intramuscular injection.
>
> Further, Applicant discloses several examples in the specification to demonstrate the relative bioavailability relating to the compositions and methods claims. However, in order to

> demonstrate relative bioavailability, Applicant must provide four variables for the bioavailability equation. Applicant's disclosure fails to demonstrate relative bioavailability in its examples and does not disclose any AUC data for either route of administration.

5. I respectfully disagree with the foregoing statements by Examiner, particularly those remarks that I have underscored above. I consider that a person of ordinary skill in the art would view the instant disclosure as fully enabling for the subject matter of the currently pending claims. In particular, a person of ordinary skill in the art, would consider that the instant specification provides clear evidence that the claimed cyanocobalamin compositions achieve "a bioavailability of cyanocobalamin when administered nasally of at least about 7% relative to an intramuscular injection of cyanocobalamin."

6. Even though explicit AUC values are not provided in the instant specification for bioavailability of cyanocobalamin delivered via intramuscular injection, these data are directly derivable from comparative data presented in the application—which data fully support the subject term "a bioavailability of cyanocobalamin, when administered nasally, of at least about 7% relative to an intramuscular injection of cyanocobalamin."

7. Literal support for the subject term is provided throughout the specification, which expressly discloses (e.g., at page 3, lines 22-24) that the cyanocobalamin solutions of the invention, when administered intranasally, achieve "bioavailability of at least 7% of the bioavailability of an intramuscular injection of cyanocobalamin."

8. This relative bioavailability characteristic of the claimed, intranasal cyanocobalamin solutions represents a standard pharmacokinetic description, such as is commonly used and widely understood in the art (see, e.g., specification at page 6, line 22 to page 7, line 13). Consistent with this common usage, the specification provides explicit methodology and results, in the form of detailed comparative bioavailability studies and data presented in the Examples, which demonstrate the relative bioavailability characteristics of the claimed solutions. The data from these examples clearly and comprehensively support this relative bioavailability characteristic in a manner that would be readily understood and practiced by persons of ordinary skill in the art.

9. For example, at page 17, under the heading "PHARMACOKINETIC RESULTS," the following description is provided:

> The relative bioavailability for the two IN formulations was 0.9715. Bioavailability when comparing treatment A (Spray) versus treatment C (IM) was 0.6105, and 0.6284 when comparing Treatment B (gel) versus Treatment C (IM).
>
> ***
>
> The pharmacokinetic profiles of the spray formulation and the gel formulation are similar for C_{max} (1480 pg/mL, 1670 pg/mL, respectively) and AUC_{0-t} (9200 pg*hr/mL, 9700 pg*hr/mL, respectively). Additionally, the median difference for Tmax between the spray and gel IN formulation was less than 15 minutes (-0.24). The C_{max} value for the IM formulation was significantly higher than the C_{max} values for the two IN formulations ($p<0.0001$).
>
> Relative Bioavailability was assessed by examining the ratio of the nasal B12 spray group mean to the reference group mean with regard to AUC. The ratio is derived by dividing the AUC IN by the AUC IM, therefore, the IM AUC is used in the equation to calculate relative bioavailability, even if it's not presented in the application. The ratio of the AUC is an appropriate way to represent bioavailability, for example 12% bioavailability is just a 0.12 ratio of the AUC and multiplied by 100 is 12%.

10. Even though these data do not expressly provide comparative AUC values for IM bioavailability of cyanocobalamin from the described studies, these values are readily and accurately derivable from the data that are presented. Persons of ordinary skill in the art would readily discern this aspect of the description, and no experimentation beyond the results provided in the disclosure would be necessary to determine the subject, relative AUC values.

11. The comparative bioavailability study results cited from the specification above, demonstrate that the "relative bioavailability" ratio of the spray versus IM, and gel versus IM, is 0.6105, and 0.6284, respectively. As the disclosure clearly indicates, these ratios were obtained by dividing the AUC of the spray, or gel, by the AUC of IM-administered cyanocobalamin. Therefore, the AUC for the IM is readily discerned based on the ratios 0.6105 and 0.6284--a simple mathematical calculation from the AUC of spray and gel and the AUC for the IM is obtained as 15000 pg*hr/ml. As the specification also clearly indicates, these data were dosed normalized according to conventional practice (to the appropriate dose multiple based on a dose of 500 μg given intranasal and 100 μg given by IM; see, e.g., pages 12-16).

12. The skilled artisan would have readily understood these data and fully appreciated that the dose normalized data fully evinced a ratio of bioavailability between the IN cyanocobalamin solutions of the invention and IM-administered cyanocobalamin—which ratio as exemplified in the disclosure is shown to correspond reasonably to the claimed value of "at least about 7%." This determination requires nothing more than a standard mathematical operation to derive the dose normalized relative AUC values for the IN spray and IM injection. In the example provided on page 17, this standard operation/result is 0.6105 X 100 µg/500 µg X100 = 12%; or a ratio of the AUC between the IN spray and IM injection of 0.12. In addition to these clearly founded values, the actual arithmetic AUC are provided on page 17 of the specification for the spray and gel as 92000 and 97000 pg*hr/mL, respectively. These data, cross referenced to the corresponding data for IM-administration, likewise fully evince the corresponding AUC for the IM injected study comparator.

13. As such, the arithmetic mean of the AUC for IM is readily calculated as 15000 pg*hr/mL (derived quite simply by reverse mathematical operation from the ratios given--for example for the spray 92000/AUC IM = 0.61 ratio). When dose normalized according to the disclosure, these data correspond directly to an exemplary relative bioavailability value within the described ranges set forth in the specification (e.g., as described at page 8, lines 32-35--"wherein the solution of cyanocobalamin has a bioavailability of at least 7%, more preferably at least about 8, 9, 10, 11, 12% or more of the bioavailability of an intramuscular injection of cyanocobalamin.").

14. In view of the foregoing, I conclude that the data provided in the instant specification fully support the subject matter pertaining to relative bioavailability recited in the pending claims. The disclosure in this context is fully correlated and commensurate with the language and scope of the claims--such that skilled artisans in this field would accept the representations and data set forth in the disclosure as sufficient to satisfy the requirements articulated by the Examiner (i.e., to "enable cyanocobalamin compositions and methods of using the composition, wherein the claimed compositions yield "a bioavailability of about 7% relative to an intramuscular injection of cyanocobalamin" (Office Action at p. 3). Indeed, the data provided in the specification directly evince that the formulations and methods claimed yield a bioavailability of cyanocobalamin, when administered nasally, of at least 7% relative to an intramuscular injection of cyanocobalamin. Skilled artisans would have been readily able to

practice this aspect of the invention of claims 1-31, which I would regard as a routine undertaking in assessing pharmacokinetics and pharmacodynamics of the currently claimed formulations and methods. The instant disclosure fully conveys this subject matter in conventional terms. Implementation, practice, and validation of this aspect of the invention would not require undue experimentation, but is in fact directly demonstrated by the data and description provided in the application.

15. The comprehensiveness and accuracy of the instant disclosure regarding relative bioavailability of the claimed intranasal cyanocobalamin solutions (compared to IM delivery), is further evinced by a Phase I Pharmacokinetic Study completed on behalf of Nastech in September, 2002 (see Appendix B, attached hereto). The resulting Phase I Pharmacokinetic Study Report was submitted and favorably reviewed by the U.S. Food and Drug Administration (FDA). The FDA specifically reviewed and considered relative bioavailability data and findings between intranasal and intramuscular delivery formulations and methods, as a key aspect of this Report. The FDA reviewed and accepted these relative bioavailability data and findings, and ultimately approved Nastech's New Drug Application (NDA) for an intranasal cyanocobalamin solution (currently marketed as Nascobal®, a widely prescribed treatment for Vitamin B_{12} deficiency). The relative bioavailability characteristics of the approved Nascobal® product compared to IM cyanocobalamin formulations and methods, are fully supported by the '385 specification, and accurately recited in the currently pending claims.

16. Within my professional knowledge and duties described above, I designed, directed, monitored, and reviewed the Phase I Pharmacokinetic Study and Report (Appendix B), and thereafter participated in its submission and review by the FDA.

17. The relative bioavailability methods and results described in the '385 specification, referenced above, were taken directly taken from the Phase I Pharmacokinetic Study (compare pages 12-18 of specification, to pages 27-42 of the Phase I Pharmacokinetic Study Report (Appendix B)).

18. There are no substantive/technical deficiencies in the relative bioavailability methods and results described in the '385, compared to the corresponding bioavailability methods and results presented in the Phase I Pharmacokinetic Study Report. Although some material from the Phase I Pharmacokinetic Study Report was not incorporated into the '385

specification, such material was omitted for purposes of economy, and is in no way essential for describing or implementing the invention set forth in the pending claims.

19. Referring to the Phase I Pharmacokinetic Study Report at page 42 (§ 10.3.3), it is immediately apparent that the data and results concerning "relative bioavailability" for "IN" versus "IM" formulations in the Report are essentially the same data and results provided in the '385 specification (at page 17). Although AUC values are expressed for IN- and IM-treated subjects in the Phase I Pharmacokinetic Study Report, the expression of these values provides no additional substantive information in comparison to the data and results provided in the '385 specification. On the contrary, all essential information to determine IN versus IM AUC values found in the Phase I Pharmacokinetic Study Report were incorporated directly into the '385 specification. Persons of ordinary skill in the art, examining the pharmacokinetic data presented in the '385 specification, would immediately be apprised of the "relative bioavailability" characteristics of the claimed formulations and methods. The actual AUC values presented in the Phase I Pharmacokinetic Study Report are inherently disclosed in the '385 specification--in that persons of ordinary skill in the art could immediately determine AUC values for both IN- and IM-treated subjects based on the data provided in the '385 specification. This determination, based on a simple mathematical operation as described above, would require no additional information, nor experimentation. In other words, the data and conclusions provided in the '385 specification are for all purposes *equivalent* to the data and conclusions provided in the Phase I Pharmacokinetic Study Report--which the FDA expressly relied upon to conclude that Nascobal® achieves high, therapeutically effective, relative bioavailability compared to IM cyanocobalamin formulations and methods, consistent with the relative bioavailability terms presented in the instant disclosure and recited in the pending claims.

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20. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that I make these statements with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize validity of the application or any patent issuing thereon.

Date: _____

By: _____
Anthony Silleo, M.S.

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